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<b>(21) International Application Number:</b> PCT/US89/02874 <b>(22) International Filing Date:</b> 30 June 1989 (30.06.89)  <b>(30) Priority data:</b> 213,889 30 June 1988 (30.06.88) US  <b>(71)(72) Applicant and Inventor:</b> SHAMSUDDIN, Abulkalam, M. [US/US]; 2916 Old Court Road, Baltimore, MD 21208 (US).  <b>(74) Agents:</b> WHITE, John, L. et al.; Millen, White & Zelano, 503 Crystal Mall 1, 1911 Jefferson Davis Highway, Ar- lington, VA 22202 (US).  <b>(81) Designated States:</b> DE (European patent), FR (European patent), GB (European patent), IT (European patent), JP, SU.		<b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> REDUCTION OF CELL PROLIFERATION AND ENHANCEMENT OF NK-CELL ACTIVITY  <b>(57) Abstract</b>  A method for moderating the rate of cellular mitosis in a living mammalian tissue having a pathologically elevated rate of cellular mitosis, which comprises perfusing said tissue under mitotic growth conditions with a safe and effective amount and concentration of a composition consisting essentially of a) inositol hexaphosphate or a physiologically acceptable salt thereof; and b) a source of inositol or a physiologically acceptable salt thereof, for a period of time sufficient to moderate the elevated rate of cellular mitosis to a normal, non-pathological rate for said tissue. The method is useful in human and mammalian diseases wherein NK cell activity is altered in the laboratory, e.g. tumors, other cancers including leukemia, immunosuppressed individuals (AIDS and transplant recipients), and in viral, fungal or protozoal infections.		

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REDUCTION OF CELL PROLIFERATION  
AND ENHANCEMENT OF NK-CELL ACTIVITY

DESCRIPTION OF THE INVENTION

1. Technical Field of the Invention

5        This invention relates to compositions comprising  
a mixture of inositol (I) and inositol hexaphosphate  
(IP<sub>6</sub>) and their use in normalizing the rate of mitosis in  
mammalian tissues wherein said rate is abnormally high,  
e.g. in various cancers. This invention also relates to  
10    the use of such compositions in enhancing reduced natural  
killer cell (NK-cell) activity, e.g. in patients whose  
immune systems are abnormally suppressed due to disease  
(e.g., AIDS), chemotherapy, preparation for transplant  
reception, etc.

15    2. Background Art

Inositol (hexahydroxycyclohexane) and its phosphates  
are well known, nontoxic, naturally occurring compounds  
which have been used for a number of pharmaceutical  
applications. Inositol is a 6-carbon sugar that is

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present in both animal and plant cells, either as a part of a larger molecule, e.g. phospholipids, or in phosphorylated form, e.g. the various inositol phosphates. Inositol triphosphate (IP<sub>3</sub>) is known to be  
5 important in the regulation of cell proliferation, a key event in cancer formation; some authors have suggested that IP<sub>3</sub> causes a release of intracellular calcium, which is an essential rate regulator, bringing about cell division and proliferation; see R. A. Steinhardt & J.  
10 Alderton, Nature 332: 364 - 366 (1988).

The inositols can be commercially prepared by a number of methods, e.g. see Posternak U.S. Patent 1,313,014; Goedecke U.S. Patent 1,715,031; Wagner, U.S.  
15 Patent 1,716,286; Goedecke U.S. Patent 1,721,214; U.S. Patent 2,112,553; Elkin, U.S. Patent 2,414,365; etc.

Revici, U.S. Patent 3,470,295 describes therapeutic compositions for treating posttraumatic shock, pain and  
20 hemorrhage in which one of the compounds thereof is maltose, inositol, or sorbitol. Bodor et al., U.S. Patent 4,154,824 describe the use of the potassium salt of inositol hexaphosphate (phytic acid) in administering potassium to a mammal without imparting a metallic  
25 potassium aftertaste. Nicolau et al., U.S. Patents 4,192,869; 4,321,259; and 4,473,563, describe inositol hexaphosphate-containing lipid vesicles which are not in solution but rather fused to erythrocytes to provide improved oxygen release properties. More recently, Siren  
30 U.S. Patent 4,735,936, the contents of which are incorporated by reference herein, describes the use of inositol triphosphate or its salts in the treatment of conditions caused or aggravated by cadmium or aluminum or free radicals in the body.

5        Graf et al., in Cancer 56: 717 - 718 (1985)  
suggested a relationship between diet and colonic cancer  
in which inflammatory bowel diseases might be suppressed  
by diets rich in phytic acid, which is believed to be  
based on the suppression by dietary phytate of iron-  
catalyzed oxidative processes producing hydroxy radicals.  
Shamsuddin et al., in Carcinogenesis 9(4): 577 - 580  
10        (1988) demonstrated that there are indeed some  
correlations between dietary factors (specifically the  
effect of sodium inositol hexaphosphate or "phytate") and  
the incidence of large intestinal cancer in laboratory  
rats.

15        Cancer is, of course, well known as a major health  
problem in the world today. In spite of vast sums which  
have been spent in pursuit of remedies, very few drugs  
have been shown to be effective in either treatment or  
prevention of cancer, and those which have are for the  
20        most part characterized by their high toxicity and  
relatively poor tolerance.

#### Disclosure of the Invention

25        Accordingly, it is a general object of the present  
invention to provide a method and composition for the  
prevention and inhibition of various cancers which does  
not suffer from the above-indicated deficiencies of the  
prior art.  
30

Another object of the present invention is to  
provide a method and composition for regulating abnormal  
rates of cell mitosis which are associated with a number

of known diseases.

5 A further object of the present invention is to provide such a method and composition for therapeutic use in cases of immunosuppression, e.g., in patients having AIDS or undergoing treatment such as chemotherapy or preparation for transplant reception.

10 An additional object of the present invention is to provide such a method and composition for therapeutic use in cases of bacterial, viral, fungal, and protozoal infections.

15 A more particular object of the present invention is to provide a pharmaceutical composition suitable for use in such methods, preferably adapted for enteral or parenteral administration and especially labeled for at least one of the above uses.

20 Upon study of the specification and appended claims, further objects, features and advantages of the present invention will become more fully apparent to those skilled in the art to which this invention pertains.

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#### BEST MODE FOR CARRYING OUT THE INVENTION

30 Briefly, the above and other objects, features and advantages of the present invention are attained in one aspect thereof by providing a method for moderating the rate of cellular mitosis in a living mammalian tissue having a pathologically elevated rate of cellular mitosis (e.g., as reflected in abnormally high cell proliferation), which comprises perfusing said tissue

under mitotic growth conditions with a safe and effective amount and concentration of a composition consisting essentially of a) inositol hexaphosphate or a physiologically acceptable salt thereof; and b) a source of inositol or a physiologically acceptable salt thereof, for a period of time sufficient to moderate the elevated rate of cellular mitosis to a normal, non-pathological rate for said tissue. By the term "perfusion" as used herein is meant exposing the tissue to a solution of the active compounds, e.g. by flowing blood or any other physiologically acceptable fluid having the compounds dissolved therein across or through the tissue being treated. Generally the molar ratio of a) to b) is about 1 : 10 to 10 : 1, preferably about 1 : 3 to 3 : 1 and especially about 1 : 1.

The compounds of this invention can be employed in admixture with conventional excipients, i.e., pharmaceutically acceptable organic or inorganic carrier substances suitable for parenteral, enteral (e.g., oral) or topical application which do not deleteriously react with the pharmacologically active compounds. Suitable pharmaceutically acceptable carriers include but are not limited to water, salt solutions, alcohols, gum arabic, vegetable oils, benzyl alcohols, polyethylene glycols, gelatin, carbohydrates such as lactose, amylose or starch, magnesium stearate, talc, silicic acid, viscous paraffin, perfume oil, fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid esters, hydroxymethyl cellulose, polyvinyl pyrrolidone, etc. The pharmaceutical preparations can be sterilized and if desired mixed with auxiliary agents, e.g., lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers,

coloring, flavoring and/or aromatic substances and the like which do not deleteriously react with the active compounds. They can also be combined where desired with other active agents, e.g. vitamins.

5

For parenteral application, particularly suitable are injectable, sterile solutions, preferably oily or aqueous solutions, as well as suspensions, emulsions, or implants, including suppositories. Ampoules are convenient unit dosages.

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For enteral application, particularly suitable are tablets, dragees, liquids, drops, suppositories, or capsules. A syrup, elixir, or the like can be used wherein a sweetener is employed.

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Sustained or directed release compositions can be formulated, e.g., liposomes or those wherein the active compound is protected with differentially degradable coatings, e.g. by micro-encapsulation, multiple coatings, etc. It is also possible to freeze-dry the compounds and use the lyophilizates obtained, for example, for the preparation of products for injection.

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For topical application, non-sprayable viscous to semisolid or solid non-sprayable forms comprise a carrier compatible with topical application and having a dynamic viscosity preferably greater than water. Suitable formulations include but are not limited to solutions, suspensions, emulsions, creams, ointments, powders, liniments, salves, aerosols, etc. which are, if desired, sterilized or mixed with auxiliary agents, e.g. preservatives, stabilizers, wetting agents, buffers, salts for influencing osmotic pressure, etc. Also

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suitable for topical application are sprayable aerosol preparations wherein the active ingredient, preferably in combination with a solid or liquid inert carrier material, is packaged in a squeeze bottle or in admixture with a pressurized, volatile, normally gaseous propellant, e.g. a freon.

Oral administration is presently preferred although, depending on the location and nature of the tissue being treated, other known types of administration can be preferred, e.g. intravenous administration for treatment of blood cancers such as leukemia; parenteral administration for direction to other body fluids such as pericardial, spinal, pleural, etc.; use in a rectal enema wash for use in treatment large intestinal cancer, etc.; bladder wash or irrigation, and the like.

Generally, the compounds of this invention are dispensed in unit dosage form comprising about 0.1 to 10 g. in a pharmaceutically acceptable carrier per unit dosage. They are incorporated in topical formulations in concentrations of about 1 to 10 weight percent.

The daily dosage of the compounds according to this invention is generally about 10 to 500 mg/kg/day, preferably 50 to 100 mg/kg/day, when administered to humans to treat large intestinal cancer.

It will be appreciated that the actual preferred amounts of active compound in a specific case will vary according to the specific compound ratios being utilized, the particular compositions formulated, the mode of application, and the particular situs and organism being treated. Dosages for a given host can be determined

using conventional considerations, e.g. by comparison of the differential activities of the pharmaceutically active compounds of this invention with known agents by means of an appropriate conventional pharmacological protocol and extrapolation of the dosages based on the results thereof, as is known in the art.

In one aspect of the present invention, the pathological elevated rate of cellular mitosis is caused by cancer, e.g. cancer of the blood, i.e. a leukemia, or large intestinal cancer.

In another aspect of the present invention, the abnormally low rate of NK cell tumoricidal activity is caused by immunosuppression, which can be the result of a disease such as cancer or pharmacologically induced. Examples include but are not limited to Acquired Immuno Deficiency Syndrome (AIDS) and immunosuppression which is pharmaceutically induced in preparation for receiving a tissue transplant or by cancer chemotherapy agents commonly used today.

In another aspect of this invention, the immunosuppression is caused by a bacterial, viral, fungal, or protozoal infection. For Example, see R. Herberman and J. Ortaldo in Science 214: 24 - 30 (1981) and J. L. Marx in Science 251: 1367 - 1369 (1986), the contents of which are incorporated by reference herein.

In a compositional aspect, the present invention provides a pharmaceutical composition for moderating the rate of cellular mitosis in a living mammalian tissue having a pathologically elevated rate of cellular mitosis by perfusing said tissue under mitotic growth conditions,

for a period of time sufficient to moderate the elevated rate of cellular mitosis to a normal, non-pathological rate for said tissue, which comprises a safe and effective amount and concentration of composition consisting essentially of a) inositol hexaphosphate or a physiologically acceptable salt thereof; and b) a source of inositol or a physiologically acceptable salt thereof. Generally, the molar ratio of a) to b) is about 1 : 10 to 10 : 1, preferably about 1 : 3 to 3 : 1 and especially about 1 : 1.

The pharmaceutical compositions of the present invention can be adapted for intravenous administration as is known in the art, e.g. see Remington's Pharmaceutical Science, 15th Edition (1975), especially Part 8: Pharmaceutical Preparations and Their Manufacture, the contents of which are incorporated by reference herein. The compositions are preferably packaged in unit dosage form, e.g. 0.1 - 10 g. of active ingredient per unit dosage which can be given one or more times per day. Preferably, the composition is packaged in a sterile container and labeled for use according to the process of this invention.

While not wishing to be bound by any theory of the invention, it is presently believed that a mixture of the molecules of inositol and inositol hexaphosphate may give rise to various inositol phosphates (from the monophosphates to the pentaphosphates) in addition to the starting materials which are administered. In most biological systems, an excess of rate limiting substance enhances the rate of the reaction. Thus, one effect of the present composition on cells (whether normal or cancerous) would have been expected to be an increase in

IP3, which would result in even more cell proliferation. Paradoxically, this has not been observed and instead the mixture of inositol and inositol hexaphosphate has been shown not only to prevent cancers, but also to be effective in treatment. Furthermore, as there has been minimal or no detectable toxic effects observed in standard screening rodents, and in view of inositol's wide occurrence in nature, it would appear from such data to probably be safe for human use.

More specifically, the NK cell activity is known to be altered in tumors, in immunosuppressed individuals, and in bacterial, viral, fungal and protozoal infections. Not only does the composition of the present invention enhance NK cell activity when fed to mice in vivo, it also enhances the NK cell activity when NK cells are treated in vitro, even for a short period of time; the mixture of the present invention is more effective than either of its individual ingredients used alone. Because of its clearly demonstrated in vitro activity against a human leukemia cell line, NK cells and tumor cells, administration to patients with immunodeficiency syndromes and cancers seems clearly indicated.

#### BRIEF DESCRIPTION OF THE DRAWINGS

Referring to the annexed drawings, like or corresponding reference characters refer to like or corresponding parts in the several figures, wherein:

Figure 1 shows the inverse relationship of NK-cell activity and tumor incidence following in vivo administration of the composition of the present

invention;

Figure 2 shows the effect of inositol hexaphosphate on K-562 human leukemia cell line in vitro;

Figure 3 shows the relationship between DMH-  
5 induced tumor incidence, volume, and frequency with and without administering the composition of this invention.

#### DETAILED DESCRIPTION

Without further elaboration, it is believed that one skilled in the art can, using the preceding  
10 description, utilize the present invention to its fullest extent. The following preferred specific embodiments are, therefore, to be construed as merely illustrative and not limitative of the remainder of the disclosure in any way whatsoever. In the following Examples, the temperatures  
15 are set forth uncorrected in degrees Celsius; unless otherwise indicated, all parts and percentages are by weight.

#### EXAMPLE 1

##### Large Intestinal Cancer Inhibition in Rats

20 Following the procedures of Shamsuddin et al. in Carcinogenesis 9(4): 577 - 580 (1988), F344 rats were treated with the carcinogen azoxymethane (AOM). Ten months after the carcinogen treatment and after five

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months of IP<sub>6</sub> treatment, the results set forth in Table 1 were observed:

TABLE 1

Group	No. of Tumors in THA	Tumor Volume (cm <sup>3</sup> )	Tumor Load/Unit area of large intestine
AOM only (n=16)	7.13±0.60	0.57±0.11	0.67±0.07
AOM plus IP <sub>6</sub> (n=28)	5.18±0.58	0.20±0.06	0.38±0.05
Significance	p<0.02	p<0.01	p<0.001

## EXAMPLE 2

Large Intestinal Cancer Inhibition in Mice

Following similarly reported experimental procedures, the pre-induction inhibition of large intestinal cancer by inositol and its hexaphosphate were studied in CD-1 mice, giving the results shown below in Table 2. The only group showing statistically significant reduction in tumor incidence is Group d), with a probability of 0.138 (Fisher) and chi squared p<0.1.

TABLE 2

Treatment Group	Incidence (number of mice with tumors/total)	Frequency (number of tumors per 10 mice)	Tumor Volume (mm <sup>3</sup> )
a) DMH only	6/19 (31.6%)	6.84	56
b) DMH + IP <sub>6</sub>	4/21 (19.0%)	1.90	34.5
c) DMH + I	3/20 (15.0%)	4.00	11
d) DMH+I+IP <sub>6</sub>	2/16 (12.5%)	1.87	9
Control	0/20 (0.0%)	0.00	0

## EXAMPLE 3

Cytotoxicity of Murine NK-Cells

Using known procedures, splenic NK cells from control (untreated) mice were either tested directly (control) for cytotoxicity, or were first treated in vitro with 0.05% I plus 0.05% IP<sub>6</sub> for one hour at 37°C. Even the short term in vitro treatment greatly enhanced (66% to 94%) NK-cell cytotoxicity at all three tested Effector : Target (E:T) ratios, as shown in Table 3:

TABLE 3

In Vitro Treatment of NK Cells	E:T 150:1	E:T 100:1	E:T 50:1
No treatment	31.3±1.2	22.6±2.6	14.0±1.7
Treatment	52.0±1.6	38.3±1.4	27.2±1.8
Significance	p<0.005	p<0.005	p<0.005

## EXAMPLE 4

In vivo Cytotoxicity Tests

5 Using procedures similar to those of Example 3, the cytotoxicity of murine NK cells were assayed against YAC-1 target cells following in vivo treatment of mice which had been injected subcutaneously with 1,2-dimethylhydrazine (DMH). While either IP<sub>6</sub> or I alone had  
10 increased the baseline NK activity by approximately 40%, the combination of I - IP<sub>6</sub> increased the baseline activity by 57.8%. Likewise, the combination was most effective (~100%) in increasing DMH-induced depressed NK activity. Indeed, it had raised the activity 27% more  
15 than the non-DMH treated control animals. The results are summarized in Table 4; values are the means  $\pm$  SEM of the percent cytotoxicity at an Effector : Target ratio of 150 : 1.

TABLE 4

Injection	Supplementation in Diet Drinking Water			
	none	IP <sub>6</sub>	I	I + IP <sub>6</sub>
saline	31.3 $\pm$ 1.2	43.9 $\pm$ 2.0	44.9 $\pm$ 7.4	49.4 $\pm$ 2.9
DMH	19.4 $\pm$ 1.0	31.1 $\pm$ 1.9	32.1 $\pm$ 1.7	39.8 $\pm$ 1.6
Significance p<0.005		p<0.005	p<0.01	p<0.005

35 The preceding examples can be repeated with similar success by substituting the generically or specifically described reactants and/or operating conditions of this invention for those specifically used in the examples. From the foregoing description, one skilled in the art



to which this invention pertains can easily ascertain the essential characteristics thereof and, without departing from the spirit and scope of the present invention, can make various changes and modifications to adapt it to various usages and conditions.

### Industrial Applicability

As can be seen from the present specification and examples, the present invention is industrially useful in providing a method for moderating the rate of cellular mitosis in a living mammalian tissue having an abnormally high rate of cellular mitosis, whereby the rate can be reduced to physiologically normal ranges. The present invention is also industrially useful in providing a method for increasing the rate of NK-cell tumorigenic activity in a living mammalian tissue having an abnormally low rate thereof, whereby the rate can be increased to physiologically normal ranges. These two effects frequently but not always occur in combination.

WHAT IS CLAIMED IS:

1. A method for moderating the rate of cellular mitosis in a living mammalian tissue having a pathologically elevated rate of cellular mitosis, which comprises perfusing said tissue under mitotic growth  
5 conditions with a safe and effective amount and concentration of a composition consisting essentially of a) inositol hexaphosphate or a physiologically acceptable salt thereof; and b) a source of inositol or a physiologically acceptable salt thereof, for  
10 a period of time sufficient to moderate the elevated rate of cellular mitosis to a normal, non-pathological rate for said tissue.
2. A method according to claim 1, wherein the molar ratio of a) : b) is about 1 : 10 to 10 : 1.
3. A method according to claim 1, wherein the composition is perfused by parenteral administration.
4. A method according to claim 1, wherein the composition is perfused by oral administration.
5. A method according to claim 1, wherein the pathological elevated rate of cellular mitosis is caused by cancer or precancer.
6. A method according to claim 5, wherein the cancer is a blood cancer.

7. A method according to claim 5, wherein the cancer is large intestinal cancer.

8. A method for enhancing the rate of NK cell activity in a living mammalian tissue having a pathologically or pharmaceutically decreased rate of tumorigenic activity, which comprises perfusing said tissue under mitotic growth conditions with a safe and effective amount and concentration of a composition consisting essentially of a) inositol hexaphosphate or a physiologically acceptable salt thereof; and b) a source of inositol or a physiologically acceptable salt thereof, for a period of time sufficient to enhance the reduced rate of NK-cell activity to a normal, non-pathological rate for said tissue.

9. A method according to claim 7, wherein the molar ratio of a) : b) is about 1 : 10 to 10 : 1.

10. A method according to claim 7, wherein the composition is perfused by parenteral administration.

11. A method according to claim 7, wherein the composition is perfused by oral administration.

12. A method according to claim 7, wherein the decreased rate of NK-cell activity is caused by immunosuppression.

13. A method according to claim 12, wherein the immunosuppression is caused by an AIDS-related infection.

14. A method according to claim 12, wherein the immunosuppression is pharmaceutically induced by chemotherapy or in preparation for receiving a tissue transplant.

15. A method according to claim 7, wherein the immunosuppression is caused by a bacterial, viral, fungal, or protozoal infection.

16. A pharmaceutical composition capable of a) moderating the rate of cellular mitosis in a living

5 mammalian tissue having a pathologically elevated  
rate of cellular mitosis or of b) enhancing the rate  
of NK cell activity in a living mammalian tissue  
10 having a pathologically or pharmaceutically decreased  
rate of tumorigenic activity, said moderation or  
enhancement being accomplished by perfusing said  
tissue under mitotic growth conditions, for a period  
of time sufficient to moderate the elevated rate  
15 of cellular mitosis to a normal, non-pathological  
rate for said tissue, which comprises a safe and  
effective amount and concentration of composition  
consisting essentially of a) inositol hexaphosphate  
or a physiologically acceptable salt thereof; and b)  
a source of inositol or a physiologically acceptable  
salt thereof.

17. A composition according to claim 16, wherein  
the molar ratio of a) : b) is about 1 : 10 to 10 : 1.

18. A composition according to claim 16 adapted  
for parenteral administration.

19. A composition according to claim 16 adapted  
for enteral administration.

20. A composition according to claim 16 in unit  
dosage form.

21. A composition according to claim 16 packaged  
in a sterile container and labeled for use according  
to the process thereof.

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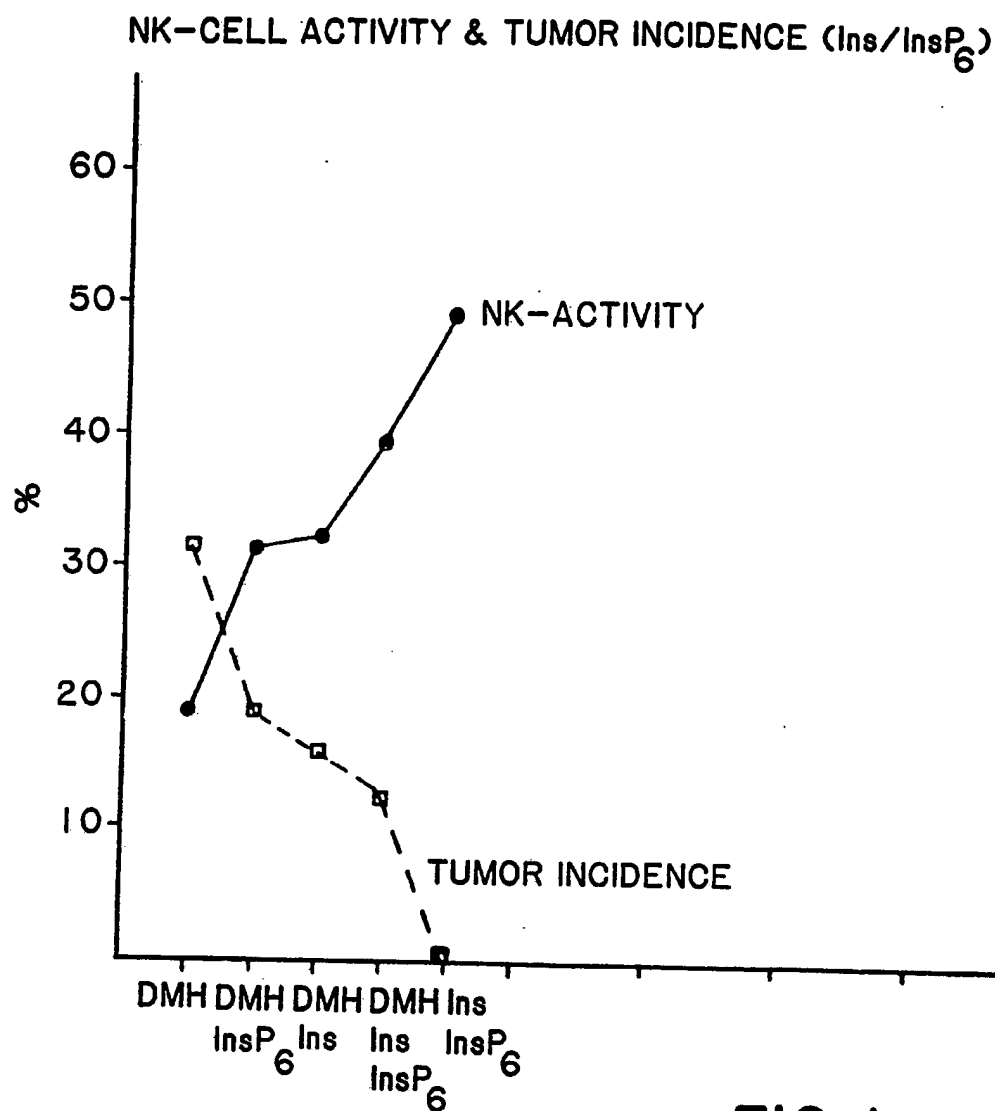


FIG. 1

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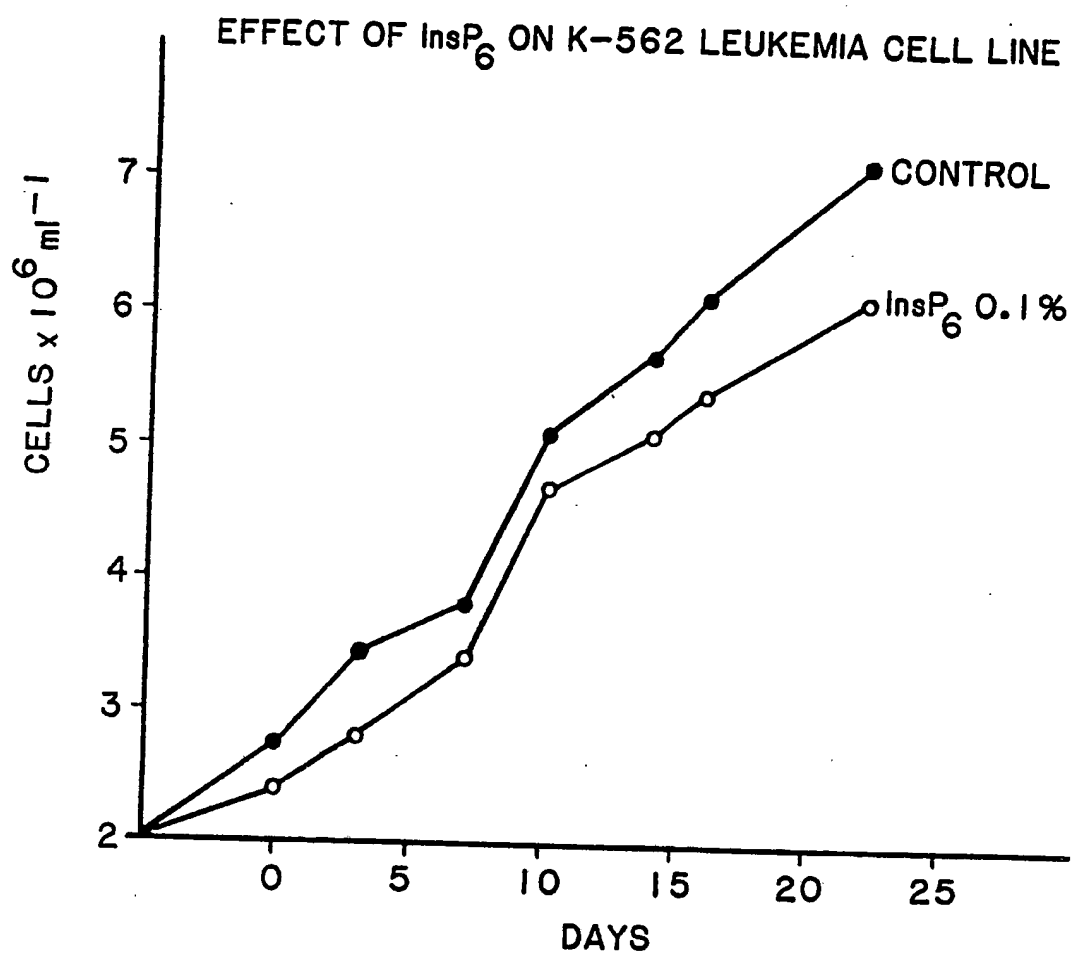
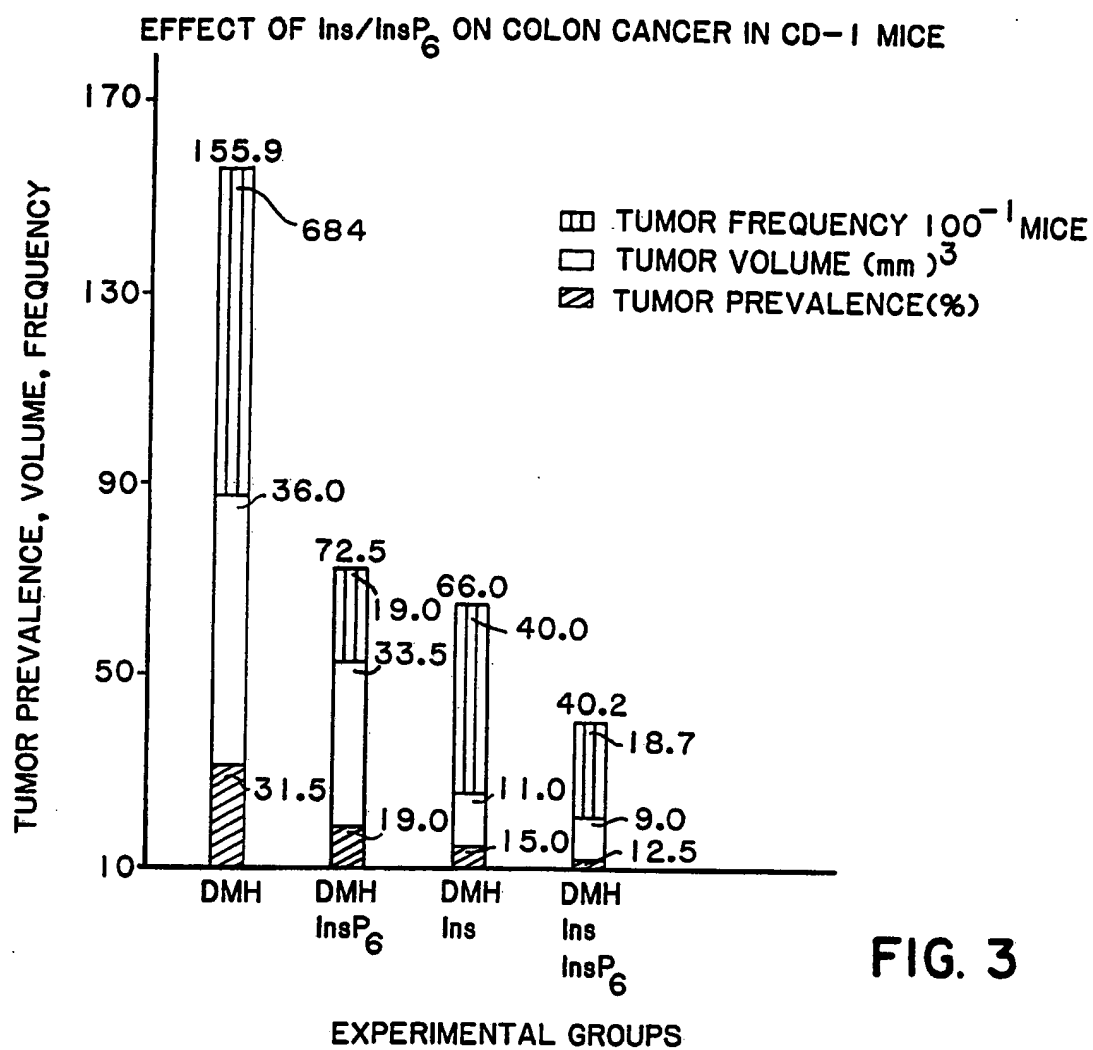


FIG. 2

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# INTERNATIONAL SEARCH REPORT

International Applic. No. **PCT/US89/02874**

<b>I. CLASSIFICATION OF SUBJECT MATTER</b> (if several classification symbols apply, indicate all) <sup>6</sup>		
According to International Patent Classification (IPC) or to both National Classification and IPC <b>IPC(4): A61K 31/66; A61K 31/045</b> <b>U.S. Cl.: 514/143; 514/729</b>		
<b>II. FIELDS SEARCHED</b>		
Minimum Documentation Searched <sup>7</sup>		
Classification System	Classification Symbols	
U.S.	514/143; 514/729	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched <sup>8</sup>		
<b>CHEMICAL ABSTRACTS-SUBJECT 1909-1988 INOSITOL AND INOSITOL HEXAPHOSPHATE</b>		
<b>III. DOCUMENTS CONSIDERED TO BE RELEVANT <sup>9</sup></b>		
Category <sup>9</sup>	Citation of Document, <sup>11</sup> with indication, where appropriate, of the relevant passages <sup>12</sup>	Relevant to Claim No. <sup>13</sup>
Y	N, DYER, 'ANINDEX OF TUMOR CHEMOTHERAPY' <u>NATIONAL INSTITUTES OF HEALTH</u> , PAGES 10-12, 151 AND 152.	1-12 AND 16-21
Y	N, ELSAYED ET AL, "INOSITOL HEXAPHOSPHATE FROM CORN DECREASED THE FREQUENCY OF COLORECTAL CANCER IN AZOXYMETHANE TREATED RATS" LAB. INVEST., VOL. 56. NO. 1, 1987, PAGE 21A.	1-12 AND 16-21
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p><sup>10</sup> Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"G" document member of the same patent family</p> </div> </div>		
<b>IV. CERTIFICATION</b>		
Date of the Actual Completion of the International Search		Date of Mailing of this International Search Report
20 September 1989		17 OCT 1989
International Searching Authority		Signature of Authorized Officer
ISA / US		JEROME D. GOLDBERG